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(54) Title: ANALOGUES OR DERIVATIVES OF QUERCETIN (PRODRUGS)

(57) Abstract

Novel carbamate ester analogues or derivatives of Quercetin (prodrugs) are provided which have enhanced aqueous solubility and which are especially suitable for use as biodegradable prodrugs in pharmaceutical compositions formulated for clinical use.

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ANALOGUES OR DERIVATIVES OF QUERCETIN (PRODRUGS)

Field of the Invention

The present invention relates to the field of biochemistry and medicine. More particularly it relates to Quercetin analogues or derivatives and preparations thereof. These compounds are potentially useful in tumour chemotherapy, treatment of inflammation and allergy.

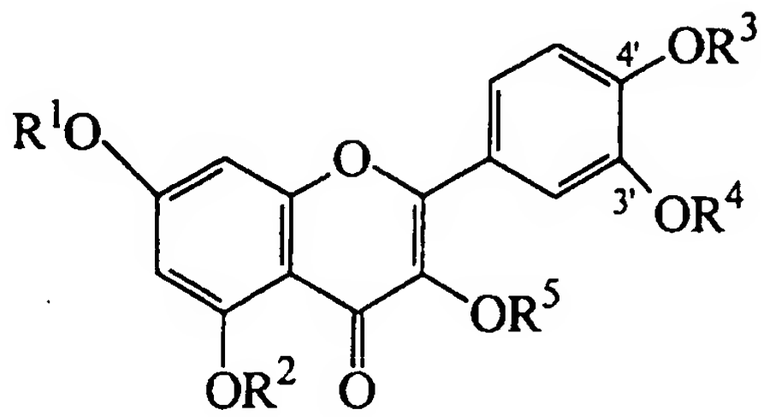
Background

The flavonoid Quercetin (3,3',4',5,7-pentahydroxyflavone) has been shown to inhibit the activity of a variety of enzymes including the calcium- and phospholipid dependent protein kinase (protein kinase C) *in vivo* and *in vitro*. Furthermore, it synergistically enhances the antiproliferative activity of cis-diaminedichloroplatinum II (cis-DDP) both *in vitro* and *in vivo* and therefore is of interest as a promising therapeutic agent for use in the chemotherapy of human tumours. However, Phase I clinical trials have proved problematic owing to the limited solubility of Quercetin in pharmaceutically acceptable solvents, and this characteristic has prevented its further clinical development.

Summary of the Invention

The present invention has developed from efforts to produce analogues or derivatives of Quercetin having greater aqueous solubility, more suitable for use in pharmaceutical formulations and capable of acting as prodrugs which can be biologically degraded or broken down to release Quercetin within the body after being administered to a patient in need of treatment.

More specifically, from one aspect, the present invention provides compounds of the structural formula I below:



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and pharmaceutically acceptable salts thereof

wherein

one of R^1, R^2, R^3, R^4 and R^5 is an amino acid carbamate group $CONHCH(R^6)CO_2H$ and the remainder are each hydrogen,

and wherein

R^6 is hydrogen or C_{1-4} lower alkyl, e.g. methyl.

Preferred compounds of this invention comprise those compounds wherein R^1, R^2, R^3 and R^5 are each hydrogen and R^4 is $CONHCH_2CO_2H$, and those compounds wherein R^1, R^2, R^4 and R^5 are each hydrogen and R^3 is $CONHCH_2CO_2H$. The invention also provides salts of these acid Quercetin analogues. Apart from alkali metal and ammonium salts, amine salts, for example amine salts formed with amino sugars, especially N-alkyl amino sugars such as N-methylglucamine, are of particular interest.

In general, the compounds of the invention as defined above are novel analogues or derivatives of Quercetin which have enhanced aqueous solubility and which are especially suitable for use as biodegradable prodrugs in pharmaceutical compositions formulated for clinical use.

Thus, the invention also includes pharmaceutical compositions comprising or containing such novel analogues or derivatives providing prodrugs made up or formulated for administration in any suitable manner in the course of medical or veterinary treatment, for example parentally (including intravenously, intramuscularly and subcutaneously) or orally. Such compositions containing or incorporating, conveniently in unit dosage form, therapeutically effective non-toxic amounts of the prodrug compound, or the equivalent of therapeutically effective non-toxic amounts of the active drug compound, together possibly with at least one other ingredient providing a compatible pharmaceutically acceptable additive, carrier, diluent or excipient, may be prepared by any of the methods well known in the art of pharmacy.

The invention also provides new processes for preparing at least some of the compounds referred to above involving in some cases certain novel intermediate compounds.

MORE DETAILED DESCRIPTION

The invention will be further described and exemplified with specific reference to the preparation and properties of Quercetin carbamate ester derivatives or analogues, particularly N-methylglucamine salts, referred to as meglumine salts, of 3'-[(N-carboxymethyl)carbamoyloxy]-3,4',5,7-tetrahydroxy-flavone and the corresponding 4' isomer.

It has been found that these carbamate esters of Quercetin are reasonably stable in aqueous solution but they will degrade to Quercetin under physiological conditions.

First, there is presented below the analytical conditions that were used to

demonstrate that the meglumine salts of 3' and 4'-[(N-carboxymethyl) carbamoyloxy]-3,4'(3'),5,7-tetrahydroxyflavone have the desired properties for formulation for clinical trial. Then, there are presented details of a process for synthesising these analogues or derivatives of Quercetin.

Analytical Methodology - Non Biological samples

The following conditions were used to analyse the meglumine salts of 3' and 4'-((N-carboxymethyl)carbamoyloxy)-3,4'(3'),5,7- tetrahydroxyflavone.

HPLC

Column:	Primesphere HC C-18, 5µm, 250 x 3.2mm.
Mobile phase:	45% Methanol in 3mM ammonium acetate pH 3.4
Flow rate:	0.5 ml/min
Temperature:	Ambient
Detection:	UV at 368nm
Injection volume:	60µl of a 100mg/ml solution in water (6µg of sample was injected onto the column; 6µg was passed through the detector and using a 1:1 splitter, 3µg was passed, in series, to the mass spectrometer.
Retention times:	Component 1 - 15.8 minutes Component 2 - 16.7 minutes

Under the same chromatographic conditions,
Quercetin has a retention time of 22.8 minutes

Mass Spectrometry

Cone voltage: 30V
Ionisation mode: Electrospray positive
Flow rate: ≅0.25ml/min (The flow was split 1:1)

Aqueous Solubility

The solubility of the meglumine salts of 3' and 4'-[(N-carboxy-methyl)carbamoyloxy]-3,4'(3'),5,7-tetrahydroxyflavone has been determined by

HPLC and shown to be in excess of 10mg/ml.

Aqueous Stability

3'/4'-((N-Carboxymethyl)carbamoyloxy)-3,4'(3'),5,7-tetrahydroxyflavone shows greater stability at acidic pH than under basic conditions. A 10mg/ml solution in water has a pH of approximately 7 and, whilst stable at -20°C for a period of at least 12 weeks, up to 25% degradation occurs at 4°C over the same period of time. Dilution into dextrose to a final prodrug concentration of 1mg/ml affords a solution with a pH of approximately 6 which undergoes less than 5% degradation over a 4h period at ambient temperature.

Stability to Human Plasma

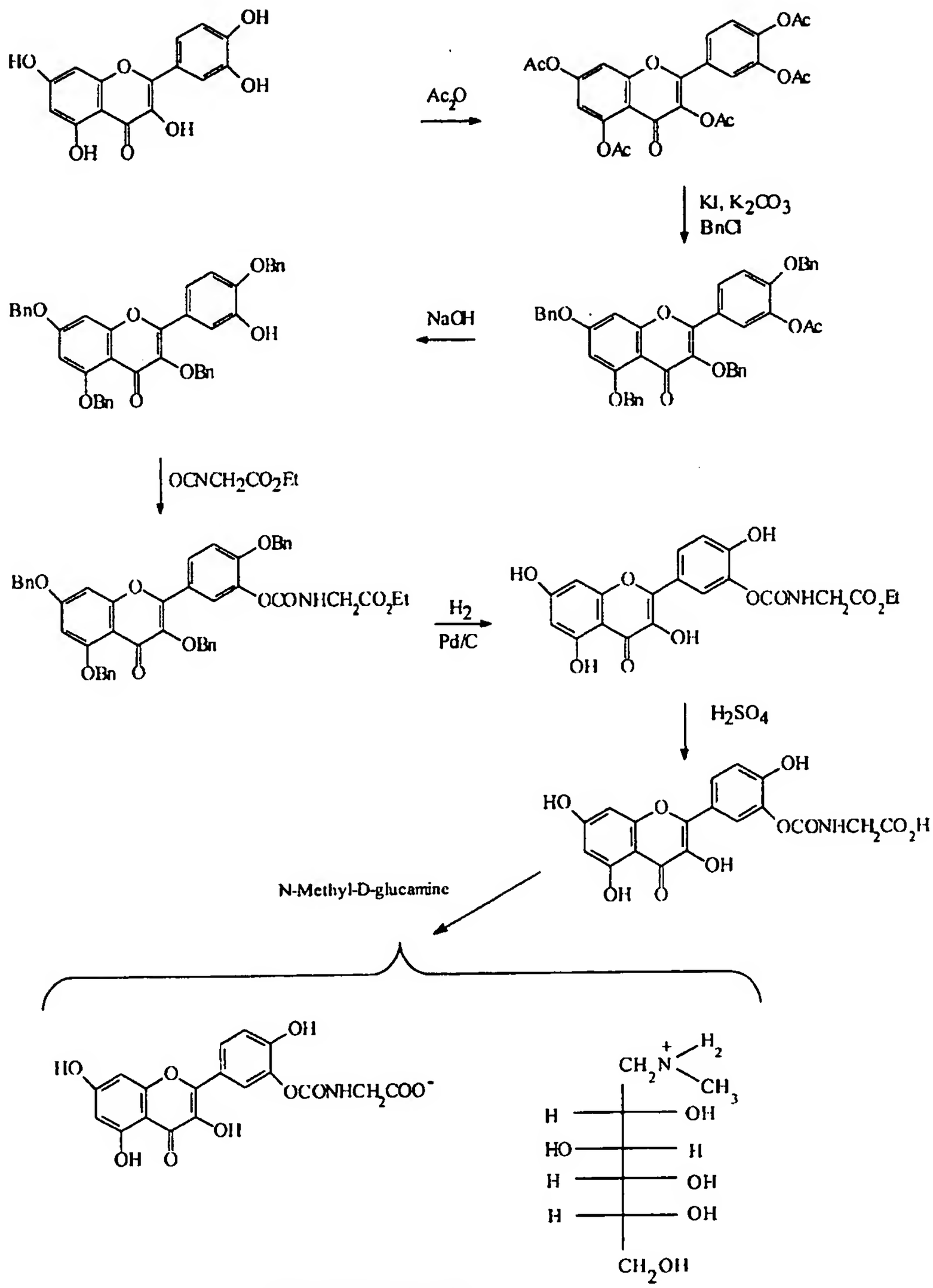
The stability of the meglumine salts of 3'/4'-((N-carboxymethyl) carbamoyloxy)-3,4'(3'),5,7-tetrahydroxyflavone has been assessed in human plasma by HPLC. Freshly prepared plasma (2.5 ml) was incubated at 37°C and 0.02ml of a 6.3 mg/ml solution of the prodrug compound in water was added. Aliquots of plasma were taken for HPLC analysis at zero time and at intervals thereafter. Samples were quenched with chilled methanol, the resulting precipitate was centrifuged at 4°C at 800rpm for 5 minutes, and the supernatant was analysed by HPLC.

Both isomers, i.e. both the 3' and 4' carbamate esters, were found to be converted into Quercetin. The half life of each isomer in human plasma was approximately 1 hour.

EXAMPLE

Synthesis of 3'/4'-((N-Carboxymethyl)carbamoyloxy)-3,4'(3'),5,7-tetrahydroxy-flavone, N-Methyl-D-glucamine salt

By way of example of the preparation of compounds in accordance with the present invention a process will now be described for the preparation of 3'/4'-[(N-Carboxymethyl)carbamoyloxy]-3,4'(3'),5,7-tetrahydroxyflavone. N-Methyl-D-glucamine salts utilising a 7-step synthesis starting from readily available Quercetin. To achieve a regioselective synthesis the acetylation/benzylation strategy originally reported by Jurd, *J.Am Chem. Soc.*, 80, 5531 (1958), was adapted to allow selective derivatisation of the 3'-position. The different steps or stages in the process are illustrated in the diagram below. Although the primary target product would appear to be the 3' isomer, it was found that after Stage 6 some migration occurs leading to formation also of the 4' isomer so that the final product is a mixture of both 3' and 4' isomers.



N-Methyl-D-glucamine salt

Stage 1 - Preparation of 3,3',4',5,7-Pentaacetoxyflavone

Concentrated sulfuric acid (ca 0.05ml) was added to an ice cold suspension of Quercetin dihydrate (50.02g, 0.15mol) in acetic anhydride (300ml) and an immediate colour change from yellow to orange was observed. The mixture was heated to 90°C for 0.25h, then cooled in an ice bath. A heavy, off-white precipitate formed which was collected by filtration, washed with water and dried *in vacuo* over phosphorus pentoxide at room temperature until no water could be detected by Karl-Fischer titration. Yield 58.1g (0.11mol, 77%).

1H-NMR (d_6-DMSO) δ DMSO = 2.49ppm: 2.32 (15H, s, 5 x CH_3), 7.18 (1H, d, J= 2.2Hz, Ar-H), 7.53 (1H, d, J= 9.2Hz, 5'-H), 7.65 (1H, d, J= 2.2Hz, Ar-H), 7.80-7.95 (2H, overlapping multiplets, 2',6'-H)

Stage 2 - Preparation of 3'-Acetoxy-3,4',5,7-tetrabenzyloxyflavone

3,3',4',5,7-Pentaacetoxyflavone (54.1g, 0.11mol), potassium iodide (4.4g, 0.026mol), potassium carbonate (127.5g, 0.92mol) and benzyl chloride (120ml) were heated at reflux in butanone (780ml) which had been dried over boric anhydride. After 48h the reaction mixture was allowed to cool to ambient temperature and filtered. The residue was washed with acetone (3 x 200ml) and the combined washings and filtrate were evaporated *in vacuo*. The evaporation residue was recrystallised twice from ethyl acetate/petrol to furnish the required product as an off white solid (62.8g, 0.089mol, 84%).

1H-NMR (d_6-DMSO) δ DMSO = 2.49ppm: 2.27 (3H, s, CH_3), 5.05 (2H, s, Ar-CH_2), 5.21 (2H, s, Ar-CH_2), 5.24 (4H, s, 2 x Ar-CH_2), 6.69 (1H, d, J= 2.0Hz, Ar-H), 6.97 (1H, d, J= 2.1Hz, Ar-H), 7.30-7.60 (20H, overlapping multiplets, Ar-H), 7.62 (1H, dd, J= 7.1Hz, Ar-H), 7.79 (1H, d, J= 2.2Hz, Ar-H), 7.91 (1H, dd, J= 2.2Hz, 8.8Hz, Ar-H)

Stage 3 - Preparation of 3'-Hydroxy-3,4',5,7-tetrabenzyloxyflavone

Aqueous sodium hydroxide solution (191ml of a 10% w/v solution) was added to a solution of 3'-acetoxy-3,4',5,7-tetrabenzyloxyflavone (61.9g, 0.088mol) at reflux in methanol/acetone (780ml of a 2:5 v/v solution). After 1h the reaction mixture was cooled to ambient temperature, diluted with water (480ml) and acidified to pH 1 with hydrochloric acid (230ml of a 2M solution). A yellow precipitate formed which was isolated by filtration, washed with water (3 x 120ml), dried *in vacuo* and recrystallised from ethyl acetate/petrol. Yield 47.4g (0.072mol, 81%).

1H-NMR (d_6-DMSO) δ DMSO = 2.49ppm: 4.98 (2H, s, Ar-CH_2), 5.21 (2H, s, Ar-CH_2), 5.23 (2H, s, Ar-CH_2), 5.26 (2H, s, Ar-CH2), 6.70 (1H, d, J= 2.0Hz, Ar-H), 6.89 (1H, d, J= 2.0Hz, Ar-H), 7.28-7.58 (20H, overlapping multiplets, Ar-H), 7.62 (2H, dd, J= 7.1Hz, Ar-H), 9.4 (1H, bs, -OH)

Stage 4 - Preparation of 3'-((N-Ethoxycarbonylmethyl)carbamoyloxy)-3,4',5,7-tetrabenzyloxyflavone

Triethylamine (11ml) and ethyl isocyanatoacetate (11.8ml, 13.6g, 0.11mol) were added to a suspension of 3'-hydroxy-3,4',5,7-tetrabenzyloxyflavone (46.7g, 0.071mol) in tetrahydrofuran (425ml) and the mixture was stirred at 50°C. After 0.5h the suspended solids dissolved. After a further 18h a further portion of ethyl isocyanatoacetate (3ml, 3.5g, 0.027mol) was added and stirring continued. After a further 2.5h the reaction mixture was evaporated *in vacuo* and the residue was recrystallised from dichloromethane/petrol to furnish N,N'-di(ethoxycarbonylmethyl)urea. The supernatant liquor was evaporated and the residue was recrystallised from ethyl acetate/petrol to furnish the title compound as a white solid (36.5g, 0.046mol, 65%)

1H-NMR (d_6-DMSO) δ DMSO = 2.49ppm: 1.19 (3H, t, J= 7.1Hz, CH_3), 3.88 (2H, d, J= 6.0Hz, NHC$\underline{H}_2$), 4.12 (2H, q, J= 7.1Hz, -OCH_2-), 5.03 (2H, s, Ar-CH_2), 5.23 (2H, s, Ar-CH_2), 5.25 (2H, s, Ar-CH_2), 5.26 (2H, s, Ar-CH_2), 6.70 (1H, d, J= 2.0Hz, Ar-H), 7.02 (1H, d, J= 2.0Hz, Ar-H), 7.28-7.58 (19H, overlapping multiplets, Ar-H), 7.63 (2H, d, J= 6.9Hz, Ar-H), 7.81 (1H, d, J= 2.2Hz, Ar-H), 7.90 (1H, dd, J= 2.2Hz, 8.8Hz, Ar-H), 8.29 (1H, t, J= 6.1Hz, -NH-)

Stage 5 - Preparation of 3'-((N-Ethoxycarbonylmethyl)carbamoyloxy)-3,4',5,7-tetrahydroxyflavone

A solution of 3'-((N-ethoxycarbonylmethyl)carbamoyloxy)-3,4',5,7-tetrabenzyloxyflavone (24.6g, 0.031mol) in THF (460ml) was shaken under a hydrogen atmosphere (pH_2 = 110psi) in the presence of palladium on charcoal catalyst (10% w/w Pd, 2.5g). After 20h the reaction mixture was filtered and the filtrate evaporated *in vacuo* to furnish the title compound as a yellow solid (14.7g) which was contaminated with toluene and THF as judged by ^{1}H-NMR but was considered suitable for use without further drying.

1H-NMR (d_6-DMSO) δ DMSO = 2.49ppm: 1.22 (3H, t, J= 7.1Hz, CH_3), 3.85 (2H, d, J= 6.0Hz, NHC$\underline{H}_2$), 4.13 (2H, q, J= 7.1Hz, -OCH_2-), 6.20 (1H, d, J= 2.0Hz, Ar-H), 6.46 (1H, d, J= 2.0Hz, Ar-H), 7.06 (1H, d, J= 8.6Hz, 5'-H), 7.86-7.93 (2H, overlapping multiplets, 2',6'-H), 8.12 (1H, t, J= 6.1Hz, -NH-), 9.54 (1H, s, -OH), 10.38 (1H, s, -OH), 10.79 (1H, s, -OH), 12.43 (1H, s, -OH)

Stage 6 - Preparation of 3'-((N-Carboxymethyl)carbamoyloxy)-3,4',5,7-tetrahydroxyflavone

3'-((N-Ethoxycarbonylmethyl)carbamoyloxy)-3,4',5,7-tetrahydroxy-flavone (6.03g, 0.014mol) was dissolved in THF (400ml) and heated to reflux. Sulfuric acid (350ml of a 2M solution) was added and the reaction mixture was heated at 70°C. The progress of the reaction was monitored by HPLC (Primesphere HC C-18, 5mm 250 x 3.2mm; mobile phase: 34% acetonitrile and 0.04% trifluoroacetic acid in water; flow rate: 0.9ml/min; detection:UV at 220nm) at intervals of 0.5h: the starting ester, the required product and Quercetin were all detected in the reaction mixture. After 2h the proportion of the desired product appeared to be at a maximum. The reaction mixture was poured into water (1.5L) and extracted with ethyl acetate (500ml, 3 x 200ml). The ethyl acetate extracts were combined and washed with water (5 x 100ml), dried over magnesium sulfate and evaporated *in vacuo* to furnish the required product as a yellow solid (5.57g) contaminated with 8% w/w Quercetin and 1%w/w 3'-((N-ethoxycarbonylmethyl)carbamoyloxy)-3,4',5,7-tetrahydroxyflavone as judged by HPLC.

1H-NMR (d_6-DMSO) δ DMSO = 2.49ppm: 3.76 (2H, d, J= 6.0Hz, NHC$\underline{H}_2$), 6.19 (1H, d, J= 1.9Hz, Ar-H), 6.46 (1H, d, J= 1.9Hz, Ar-H), 7.05 (1H, d, J= 8.5Hz, 5'-H), 7.88-7.92 (2H, overlapping multiplets, 2',6'-H), 8.04 (1H, t, J= 6.1Hz, -NH-), 9.58(1H, s, -OH), 10.40 (1H, s, -OH), 10.82 (1H, s, -OH), 12.44 (1H, s, -OH), 12.5 (1H, bs, COOH)

Stage 7 - Preparation of 3'-((N-Carboxymethyl)carbamoyloxy)-3,4',5,7-tetrahydroxyflavone, N-Methyl-D-glucamine salt

A solution of N-methyl-D-glucamine (2.76g, 0.014mol) in methanol (200ml) was added to a solution of 3'-((N-carboxymethyl)carbamoyloxy)-3,4',5,7-tetrahydroxyflavone (5.78g, 90% pure, 0.013mol) in methanol (300ml). The solvent was removed *in vacuo* and the residue was dissolved in water (500ml). The solution was adjusted to pH 6.9 with 1M hydrochloric acid, extracted with ethyl acetate (3 x 50ml) and freeze dried. The freeze dried solid was redissolved in water (500ml) and filtered successively through 1.2µm, 0.45µm, and 0.2µm filters and freeze dried once more to furnish the required product as a fine yellow solid (6.12g, 0.01mol, 79%)

1H-NMR (D_2O) δ HOD = 4.8ppm: 2.69 (3H, s, NCH_3), 3.13 (2H, bm, CH_2NHCH_3), 3.5 - 3.8 (7H, overlapping multiplets, CHOH), 4.01 (1H, m, CHOH), 5.80 (2H, bd, Ar-H, both isomers), 6.67 (1H, d, Ar-H, major isomer), 6.90 (1H, d, Ar-H, minor isomer), 7.20 (2H, overlapping multiplets, Ar-H, minor isomer), 7.41 (2H, overlapping multiplets, Ar-H, major isomer).

IR (KBr disc) ν = 3360 (OH, NH), 2931, 1715 (C=O), 1655 (C=O), 1598 (C=O), 1561, 1514, 1461, 1424, 1383, 1315, 1248, 1189, 1166, 1087, 1043cm^{-1}

FAB _m/z= 635, 599 $((M+H)^+)$, 598 (M^+), 586, 460, 440, 427, 404, 391, 307, 303, 287, 196 (N-methylglucamine + H)$^+$

Although the final product is a mixture of the 3' and 4' isomers, these can be separated if desired, e.g. by HPLC, but since both can act as prodrugs that degrade to Quercetin, separation will generally be unnecessary. The final product may also contain a certain amount of the N-methyl-D-glucamine, but again this is

considered unlikely to interfere with the desired Quercetin prodrug characteristics of the product.

N-alkylated carbamates for use in other embodiments where R^6 is alkyl may be prepared by reaction of phenols with reagents of the type RR'NCOCl which are conveniently prepared *in situ* by reaction of the appropriate amine with phosgene. Alternatively they may be prepared by reaction of amines of the type RR'NH with aryl chloroformates ArOCOCl, which are themselves prepared *in situ* by reaction of phenols with phosgene. Thus $ArOC(O)NRCH_2CO_2Et$ for example may be prepared by reaction of ArOH with $RNHCH_2CO_2Et$ in the presence of phosgene or triphosgene.

In preparing amine salts of Quercetin analogues or derivatives in accordance with the invention using an amino sugar, various amino sugars other than the N-methyl-D-glucamine hereinbefore mentioned may of course be used instead. A non-exhaustive list of amino sugars suitable for forming such salts is given below

A 1-Amino-1-deoxy-D-sorbitol

B N-Methyl-D-glucamine (meglumine)

C 1-Deoxy-1-(methylamino)-D-galactitol

D 1-Deoxy-1-(octylamino)-D-glucitol

E 1-Deoxy-1-(2-hydroxyethylamino)-D-glucitol

F Disorbitylamine

G D-Galactosamine

H D-Glucosamine

I D-Mannosamine

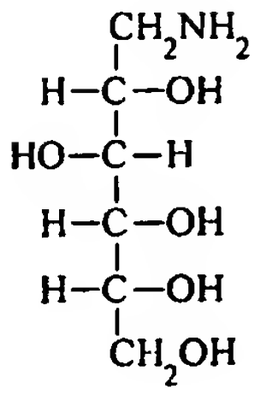
The structures of the above compounds A-I are illustrated in the diagrams at the end of the present description which are labelled to correspond.

Therapeutic Use

As already indicated, the novel analogues or derivatives of Quercetin provided by the present invention, especially such analogues or derivatives which are biodegradable *in vivo* to Quercetin and which are soluble in water, are particularly useful as prodrugs that may be made up into pharmaceutical formulations for administration in therapeutic treatment, for example therapeutic treatment of mammals suffering from neoplastic diseases or cancer.

In making up such pharmaceutical formulations in the form of sterile liquid preparations for parental use for instance, a predetermined therapeutically effective non-toxic amount of the particular analogue or derivative concerned may be dissolved in phosphate buffered saline and the preparations may be presented in unit dosage form and contained in sealed ampoules ready for use as an intravenous infusion. In general, at least in aqueous solution, concentrations equivalent to those that have been used for Quercetin will be preferred, but the amount and dosage routine required for optimum effectiveness will of course vary and is ultimately at the discretion of the medical or veterinary practitioner treating the mammal in each particular case.

As will be seen, the invention provides a number of different aspects and, in general, it embraces all novel and inventive features and aspects, including novel compounds, herein disclosed either explicitly or implicitly and either singly or in combination with one another. Moreover, the scope of the invention is not to be construed as being limited by the illustrative examples or by the terms and expressions used herein merely in a descriptive or explanatory sense.



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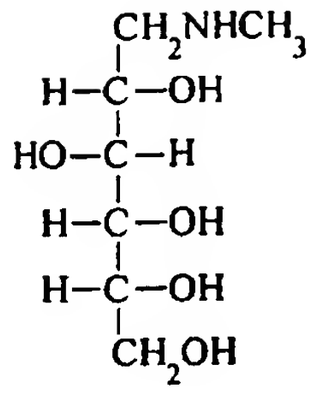

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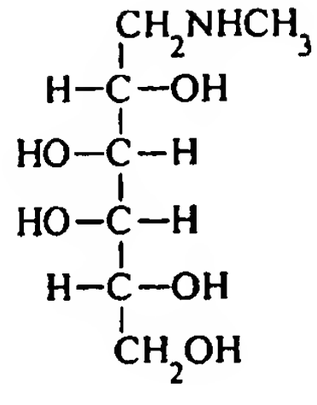

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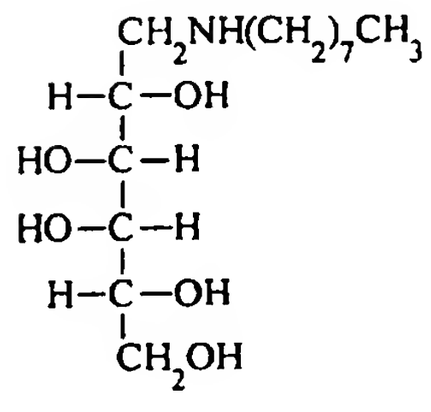

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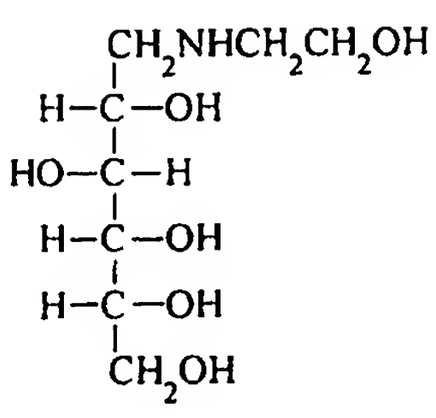

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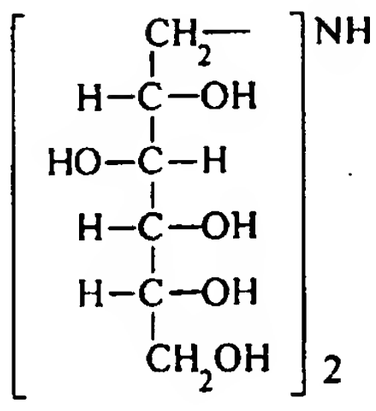

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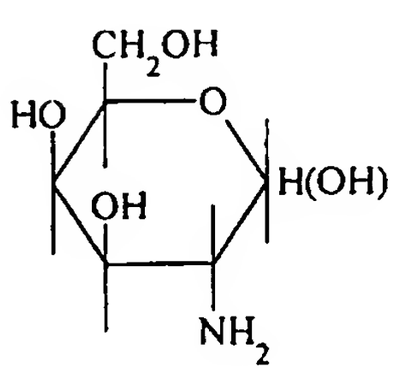

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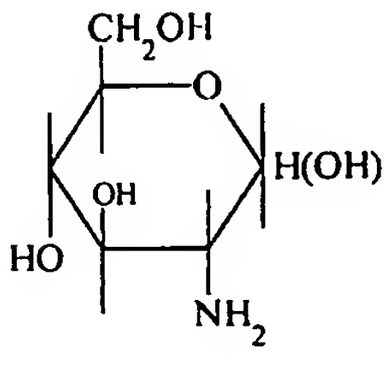

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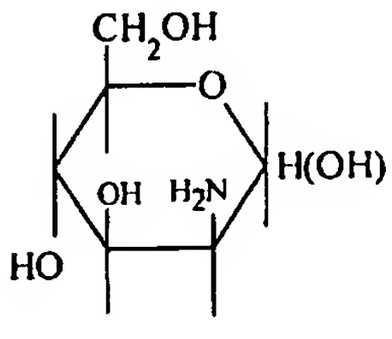

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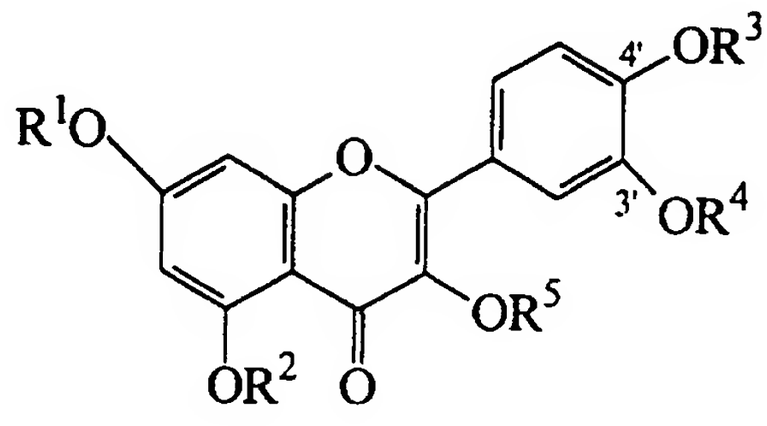
CLAIMS

1. A compound having the structural formula I



I

or a pharmaceutically acceptable salt thereof,

wherein

one of R^1, R^2, R^3, R^4 and R^5 is an amino acid carbamate group $CONHCH(R^6)CO_2H$ and the remainder are each hydrogen,

and wherein

R^6 is hydrogen or C_{1-4} lower alkyl.

2. A compound as claimed in Claim 1 wherein R^6 is methyl.

3. A compound as claimed in Claim 1 or 2 wherein R^1, R^2, R^3 and R^5 are each hydrogen and R^4 is CONH CH_2 CO_2H.

4. A compound as claimed in Claim 1 or 2 wherein R^1, R^2, R^4 and R^5 are each hydrogen and R^3 is CONH CH_2 CO_2H.

5. A compound as claimed in any of Claims 1 to 4 in the form of an alkali metal salt, an ammonium salt or an amine salt.

6. A compound as claimed in Claim 5 which is an amine salt formed with an amino sugar.

7. A compound as claimed in Claim 5 which is an amine salt formed with an N-alkyl amino sugar.

8. A compound as claimed in Claim 7 wherein the amino sugar is N-methyl-D-glucamine.

9. A compound as claimed in Claim 6 wherein the amino sugar is selected from

1-Amino-1-deoxy-D-sorbitol,
N-Methyl-D-glucamine (meglumine),
1-Deoxy-1-(methylamino)-D-galactitol,
1-Deoxy-1-(octylamino)-D-glucitol,
1-Deoxy-1-(2-hydroxyethylamino)-D-glucitol,
Disorbitylamine,
D-Galactosamine,
D-Glucosamine and
D-Mannosamine.

10. A prodrug composition comprising a mixture of a compound as claimed in any of Claims 5 to 9 wherein R^4 is CONH CH_2 CO_2H and a compound as claimed in any of Claims 5 to 9 where R^3 is CONH CH_2 CO_2H.

11. A prodrug composition comprising a mixture of 3'-((N-carboxymethyl)carbamoyloxy)-3,4',5,7-tetrahydroxyflavone, N-Methyl-glucamine salt and 3'-((N-carboxymethyl)carbamoyloxy)-3,3',5,7-tetrahydroxyflavone, N-Methylglucamine salt, biodegradable to Quercertin.

12. Use of a compound as claimed in any of Claims 1 to 9, or of a composition as claimed in Claim 10 or 11, in therapy for the treatment of mammals suffering from a neoplastic disease or cancer.

13. A pharmaceutical composition comprising a therapeutically effective non-toxic amount of a compound as claimed in any one of Claims 1 to 9, or of a prodrug composition as claimed in Claim 10 or 11, in admixture with a compatible pharmaceutically acceptable additive, carrier, diluent or

excipient.

14. A pharmaceutical composition as claimed in Claim 13 containing a Quercertin carbamate ester that is biodegradable *in vivo* to Quercertin.

15. A pharmaceutical composition as claimed in Claim 13 or 14 in the form of a sterile liquid preparation presented in unit dosage form.

16. A pharmaceutical composition as claimed in Claim 15 in which said compound or prodrug composition is dissolved in phosphate-buffered saline.

17. A method of treating a mammal suffering from a neoplastic disease or cancer comprising administering to said mammal a pharmaceutical composition as claimed in any one of Claims 13 to 16.

INTERNATIONAL SEARCH REPORT

Interna..ual Application No
PCT/GB 97/01727

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D311/30 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 505 937 A (GEYMONAT SPA) 30 September 1992 see the whole document ---	1-16
X	US 4 202 825 A (AEDO DIONISIO M ET AL) 13 May 1980 see the whole document ---	1-16
Y	EP 0 019 081 A (HOFFMANN LA ROCHE) 26 November 1980 see the whole document ---	1-16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1997	03. 12. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

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INTERNATIONAL SEARCH REPORT

Intern...onal Application No
PCT/GB 97/01727

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Y	UEDA,I. ET AL.: "Design, Synthesis And Antiinflammatory Activity of a New Indomethacin Ester. 2. 2-[N-[3-....." CHEM.PHARM.BULL., vol. 39, no. 3, 1991, TOKYO, pages 679-684, XP002044332 see the whole document ---	1-16
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PCT/GB 97/01727

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